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Dr. Alex Compton Oral History

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Dr. Alex Compton

Behind the Mask Interview

November 19, 2020

Barr: Today is November 19, 2020, and I [Gabrielle Barr] have the pleasure of speaking to Dr. Alex Compton. Dr. Compton is the head of the Antiviral Immunity and Resistance Section of the HIV Dynamics and Replication Program at the National Cancer Institute (NCI). Thank you for being with us today and talking with us about some of your coronavirus research. So, Dr. Compton, our first question is what is so important about the interferon-induced transmembrane protein 3 [IFITM -3] and why do you and your team believe that this protein can be both an asset against coronavirus infection while at times it can also be an agent for spread?

Compton: The IFITM proteins, in general, and IFITM-3 have previously been shown to be important for controlling respiratory virus infections, principally influenza. So, before COVID-19 there were a lot of us that were engaged with influenza research and worried about influenza because it causes a yearly health burden. We're also afraid of newly emergent strains of influenza that come from other animal reservoirs. It had been previously shown that a genetic variant found within the IFITM-3 gene predisposes people to having a more severe disease following influenza infection. This was specifically in 2009 with the H1N1 pandemic that emerged at that time. So, we've been interested in understanding why this genetic variant in IFITM-3 is associated with disease.

Most recently this same genetic variant has been associated with severe COVID-19 so this kind of just reinforces that this gene is particularly important. It must have some importance in vivo for controlling these virus infections, not just one virus infection but multiple virus infections. Work in my lab has shown that this is an antiviral factor that is active against a wide variety of viruses, not just these respiratory pathogens but also HIV [the virus that causes AIDS]. That's one of the reasons why we study it in my lab— it has this very broad antiviral activity. Not only does that make it fascinating but we want to better understand it on a molecular level because if we can understand how something like this inside of our cells can inhibit so many different viruses, we can take advantage of that knowledge for new antiviral therapies in terms of applying our knowledge to the COVID-19 pandemic. The fact of the matter is that all we knew is that this genetic variant is associated with more severe disease and we did not know why. We simply wanted to do those first set of experiments to better understand whether this is an antiviral gene that is active against Sars-CoV-2, the cause of COVID-19, and what type of impact it has on cells that are physiologically relevant for infections in our bodies.

Barr: Interesting. So what are the properties of this gene that causes it to behave in these different ways?

Compton: On one hand, we've shown that IFITM-3 does act as an antiviral factor and that it can inhibit Sars-CoV-2 infection—using some tricks in the lab, we also found that it's capable of promoting Sars-C0V-2 infection. That is kind of at the heart of your question. The question is how can one factor inhibits and promotes at the same time?

The key to understanding this, which is not entirely understood yet, is that this is a protein inside of our cells that has a dynamic location. It's moving around and it occupies different sites inside of our cells and this has to do with the normal trafficking pattern that our cells use. So, this is a transmembrane protein as the name implies. What that means is it's actually embedded inside of the membranes in our cells. By membranes, I mean a lipid bilayer that surrounds certain organelles inside of the cell but also surrounds the cell surface of the cell itself. So, this is a protein that is inside of these membranes but these membranes, just like cars on the highway, will move throughout the cell, back and forth, because they perform different functions at different sites. What we found is that IFITM-3 on the interior of the cell, its membranes that are associated with endosomes, performs an antiviral function. It inhibits Sars-CoV-2 infection. However, IFITM-3 at the cell surface actually promotes Sars-CoV-2 infection. What this reveals to us is that this protein is performing two different functions that impacts Sars-CoV-2 in opposite ways. It has to do simply where this protein is and where it is encountering the virus.

Basically, this is really interesting to us because we don't know very much about how Sars-CoV-2 enters cells. We're really interested not only in these antiviral factors, like IFITM-3, but also the way viruses get into cells. What's really interesting about IFITM-3 is that it's the earliest acting antiviral factor that' s known and it's one of the only things that we know that protects us against the first step of the virus life cycle which is entry inside of cells. Viruses need to enter cells in order to have any chance at all of infecting us. It's the very first step and so it's a really critical one and it's a place in which we can intervene with new therapeutic strategies. The fact of the matter is that this is an interesting study for us because it tells us not only about the function of a cellular gene, but it tells us about how the virus likes to get into our cells.

Our study highlights that there are two routes of entry for Sars-CoV-2, one via the endosomes on the interior of the cell and another route via the cell surface at the plasma membrane. Some of this information was actually previously known, thanks to a number of coronavirology labs that have existed since the early 2000s. Our work simply builds upon that basic understanding that we had and tells us a bit more about where the virus is entering and what type of barriers it is encountering when it gets there. But to really address your question about why the cellular gene is capable of performing two opposite functions during virus infection; we know more about how it's inhibiting the virus; we know various mechanistic details about how that inhibition is happening; but we know almost nothing about how it can promote virus infection at the cell surface. The latter is a totally new direction and we have really nothing to say about how that's happening other than sheer speculation and guesswork.

Barr: This is my novice knowledge, but is it like chemical differences between the inside the cell versus the chemical makeup of the outside of the cell? Do you think that plays a role?

Compton: That's a good point. That could partially explain what we're observing, and I guess in terms of the chemistry that's important for virus entry. What I would be looking at are the lipid composition of the membranes and how they distinguish each other between endosomal membranes and the plasma membranes at the cell surface. There will be distinct lipids present in those different sites and that could impact not only how the virus enters at those membrane sites but how the activity of IFITM-3 manifests. That is a really interesting idea and it's something we need to look into more carefully.

As an example, things like cholesterol will concentrate in certain parts of the cell in certain membrane domains and they'll be almost absent from other membranes. The fact is lipid composition is certainly something that we should be looking at, but, in addition to that, the protein content of membranes is also important to the biology of our cells. Viruses need to interact with cellular proteins and membranes in order to initiate the entry process into cells. The entry step that viruses use starts with just being able to stick to the cell to attach to it, to bind to it, and it could be that IFITM-3 at the cell surface, for one reason or another, is actually promoting the ability of the virus to engage the cell, to initially lock on to it, which will only facilitate all of the subsequent steps that the virus needs to do in order to get inside and to properly infect the cell. It's also possible that IFITM-3 at the cell surface is impacting proteins there such as the receptor or proteases that Sars-CoV-2 needs in order to enter the cell. In that regard, we are talking about ACE2 which is the primary receptor for the virus and proteases such as TMPRSS2 which we look at in our paper. It's possible the IFITM-3 is promoting the entry process at the cell surface by affecting some aspects of ACE2 or some aspect of TMPRSS2.

Barr: This is somewhat related. Why does IFITM-3 react differently with different types of coronaviruses?

Compton: We think that our study actually starts to paint a picture as to why that is the case. To provide a little bit of context, it was previously shown that IFITM-3 promotes the entry of a seasonal coronavirus in humans known as OC43. This was a really important observation made several years ago that really helped guide us for our studies with Sars-Cov-2. This might be the case for one coronavirus, but not the others. As I told you, for Sars-CoV-2, we know that the net effect of IFITM-3 is inhibition of virus infection but that's not the case for this other coronavirus OC43 which causes cold-like symptoms in humans. We also know that the first Sars virus, which we call Sars-CoV, which emerged in the early 2000s, is also inhibited by IFITM-3. So we now have a growing list of coronaviruses in humans, some of which are inhibited, some of which are promoted by IFITM-3, but actually our study points to a slightly more complex model where it is not a black and white situation for any given virus.

What's probably happening in our cells is that IFITM-3 can both inhibit and promote within the same cell. That's happening because IFITM-3 is at different places inside the cell, as mentioned, it could be in endosomes or the cell surface. Now, if we reexamine the relationship between IFITM-3 and these other coronaviruses, it's quite possible that we'll find that there's both an inhibition occurring and promotion. That's kind of important because in virology sometimes we're using these bulk assays with a lot of cells and one simple readout at the end. If we were just looking at that, we wouldn't know that to be this duality of function. What's kind of useful about the methods we used in the paper is that we're looking at infections in individual cells and we're looking at that infection on a molecular level.

Barr: Can you talk more in detail about how you're doing that and going about that?

Compton: The fact is this paper resulted from a collaboration between my lab and a lab at Ohio State University [OSU] led by Jacob Yount. In both cases, we use slightly different approaches to study how Sars-CoV-2 enters cells, and, therefore, slightly different systems for studying how IFITM-3 performs its activity. It's our kind of overall consensus from these different types of data that lead us to our model.

In my lab, because I am a part of this HIV Dynamics and Replication Program, we have a lot of retrovirus tools that we use for our studies. In general, how we approach studying Sars-CoV-2 infection was actually to modify HIV so that it was decorated with the spike protein of Sars-CoV-2, the spike protein being the viral protein that allows the virus to attach and to enter cells. So in our hands we used this HIV and we set up a cellular assay to watch that hybrid virus enter cells. Those cells were modified to either express IFITM-3 or not and in some cases to express IFITM-3 mutants or other IFITM proteins that are related to IFITM-3. In our lab in Frederick, we were using that system to explore the relationship between IFITM-3 and the virus. It's important to recognize that that is a purely artificial system that is designed not to recreate what's happening in nature, but to create these genetically tractable systems to understand things on a really fine molecular level. We knew from the beginning that we wanted to collaborate with others who were capable of working with the genuine virus that can replicate in cells under biosafety level three conditions, and, because we had a prior relationship with this lab at OSU, it was very easy for us to agree to do a combined study.

I'll tell you a little bit more about the two assays we use. As I mentioned, in my lab we were using HIV decorated with Sars-CoV-2 spike and watching it enter cells. The assay that allows us to see the infection happening involves a reporter gene, luciferase. How this works is basically we produce this hybrid HIV that is replication incompetent, meaning it cannot perform a spreading infection as it only gets the chance to infect cells one time. For that reason, it's considerably safer on a biosafety level. But it's carrying in its genetic components a luciferase gene and luciferase is simply an enzyme that allows for this light producing reaction that we can see inside of cells. The basic idea is this: If this hybrid HIV is able to penetrate the cells in our [petri] dishes and do so successfully, those cells will light up and all we have to do is quantitatively collect that information, that emission of light and report our findings.

Barr: How have you been collecting quantitatively the light?

Compton: It has to do with this luciferase enzyme and the chemical reaction that it produces. It's more or less a normal dish. Imagine: transparent plastic. For the most part, the dishes are not necessarily central here and the cells aren't special in the sense that it's not something that we've modified in the cells to allow this process to happen. How this works is it's simply the delivery of the luciferase gene, and therefore the enzyme that it encodes, inside of cells. If luciferase is present inside of these cells, they'll be ready and able to perform this enzymatic reaction and all we have to do to facilitate this is add a substrate called luciferin. Basically, once luciferin and luciferase find each other, luciferase can perform this job, modify the substrate, and light is emitted. So, it's simply by adding these components to cells that we make the cells light up in the presence of a virus entry.

What's cool is that with our collaborators at OSU, they had a completely different way of assessing virus entry and that's part of the strength of our study—never concluding on something scientifically by using just one approach. So, what they were using, which is great, which is also an assay that we use for our study of other viruses, is called flow cytometry. What this involves is the addition of genuine Sars-CoV-2 to cells in the same type of dish that we use, because instead of some type of light reaction, you simply need to look for evidence of viral proteins being made in those cells. These viral proteins being synthesized and produced and accumulating will be a sign that virus entry and virus infection has occurred. We use flow cytometry because it's a way to look for specific viral proteins inside of individual cells. A flow cytometer is simply something that is used to interrogate individual cells, one at a time in a stream of liquid. This is great because we can look at individual cells and we can use specific antibodies for viral proteins to assess whether that protein is present or not. Via this presence or absence assay we can say just how much infection is happening. We were able to take our results using an artificial HIV hybrid system with the system used at OSU to really find common ground and to find a mechanism.

Barr: Were there any differences between what you did and what they did that you are trying to reconcile?

Compton: We've already somewhat reconciled those differences, but we may never know why these differences exist. What we've noticed is that some of the things we were seeing using the HIV hybrid virus encoding Sars-CoV-2 did not recapitulate what was observed using real Sars-CoV-2. For example, just the ability for the virus to infect a given cell line can be very different between the two systems and that's not totally surprising, but it really is important to take note of because we use HIV and this type of pseudovirus production for biosafety reasons and for reasons of tradition and convenience, but we know that it does not perfectly recapitulate the biology of Sars-CoV-2.

So we know it has major limitations and one of the limitations that is apparent now is that the Sars-CoV-2 spike protein, which is really important for the virus to enter cells, probably does not assemble and function naturally in HIV. This is a Sars-CoV-2 protein that prefers to interact with and assemble with the other viral proteins that it knows. The fact is that spike function is modulated depending on whether it's in the presence of HIV or in the presence of the genuine Sars-CoV-2 virus.

We know that the HIV-based approach is certainly limited and that's why from the beginning we knew that we did not want to generate data solely with that system. We didn't really know just how limited it would be. In a different world it could have been perfectly comparable to what we see with Sars-CoV-2 infection but the fact of the matter is the HIV-based system is really useful for understanding mechanisms because we can use all these tools that were previously applied to HIV. So, one example is that, as I've mentioned, this luciferase gene. We already have these constructs of HIV modified to express luciferase and that's why we use this system. We also have other systems that allow us to look at specifically different aspects of the virus entry process which are not going to be observed with the OSU [system], so we can and we're still actually using HIV to look at a specific stage of virus entry which is called fusion. Fusion is where the viral membrane fuses with the cellular membrane and it's actually for this kind of virus a really crucial step for getting inside of our cells. We know we do not have any tools available to us yet to study the fusion process using genuine cryoscopy too. We have to use those model systems, for example, those based on and off of HIV in order to examine this.

So this is an example that at this stage we really benefit from having these tools derived from HIV. Even though we know that there's going to be some differences in terms of the biology that we're studying, so what we're actually interested in doing is moving into new types of systems that allow the safe manipulation of Sars-CoV-2. Just one final word about that, what will probably end up happening is that we will study Sars-CoV-2 spike in the context of a different coronavirus, so instead of HIV we use a seasonal coronavirus that's been in humans for quite some time and which doesn't cause severe disease. Therefore, we can probably reconstitute a virus that is a little bit more natural and that's going to allow the spike proteins to behave in the normal natural way and so we're really interested in the next step. We'll probably always take advantage of these HIV tools, but the fact is just like any good study, we're going to use a handful of different techniques to understand something really closely. This is just an example of how HIV researchers are going to be building their tool kits to involve other things that they never imagined having in their freezers.

Barr: What surprised you about your preliminary study? You mentioned some of the challenges but were there other challenges?

Compton: I'll start with the challenges. It was challenging to infect cells in the beginning even using genuine Sars-CoV-2. We are unsure why that is, but it's really limiting in terms of what we can learn from our systems inside the lab and the pace at which we generate results. But over the course of six months, we steadily improved our ability to observe an infection in the laboratory.

We got to the point where we achieved just enough infection to really feel confident about what we were measuring. In virology, you're interested in studying virus infection of cells that are actually physiologically relevant to the disease in humans. For something like Sars-CoV-2, that means the respiratory tract, both the upper and lower tracts, for example, in the lower respiratory tract you have the lungs and all the different cell types that make up the lungs. We've tried to infect lung cells in the lab and to study the biology going on there. We can do so but only with a certain amount of success. It turns out that the virus just has a lot of difficulty getting inside of those cells which, in my opinion, is both unfortunate but is also the chance for a new discovery. For example, we want to know why it's hard for the virus to get into those cells. To us what that indicates is that there are barriers inside of the cells in the form of antiviral factors or an absence of something the virus needs. Those are important presence and absence studies that we need in order to understand Sars-CoV-2 biology. That's an example of the types of challenges.

The most interesting and surprising finding from the paper though, is that IFITM-3 inhibits influenza very potently but Sars-CoV-2 less so. Our data shows us that IFITM-3 can inhibit Sars-CoV-2 via a mechanism that is distinct from how it inhibits influenza A virus. This was really surprising.

How we came to that conclusion is by mutating a part of IFITM-3 in a region that was previously shown to be really important for the restriction of influenza A virus—specifically these mutations modify cysteine amino acids and what happens is that those residues can no longer be modified with lipid, a process known as palmitoylation. It's a specific lipid attachment to the protein which was previously thought to allow IFITM-3 to anchor into cellular membranes. Previously, it was shown that that modification was really essential for activity against influenza A virus, and here in this study we show that inhibition of Sars-CoV-2 occurs despite the absence of those critical residues, which means that in the absence of palmitoylation, IFITM-3 can still inhibit Sars-CoV-2. That's really surprising and it tells us that what we are seeing with our eyes in the lab is a function that is distinct from what was known about restriction of influenza virus. So, we're left with a lot of new information and still a lot of unknowns.

Barr: For your next study you said that you were going for the follow-up to what you've been doing, that you're going to be testing it in a seasonal coronavirus. Do you have ideas which one as they seem to behave differently?

Compton: This is where I will defer or draw inspiration from our colleagues. This concept was not my idea but it's something I've been hearing from top virologists over the past couple of months. The idea of making a hybrid coronavirus that is safe to use in our laboratories would involve starting with the MHV [mouse hepatitis virus] coronavirus, which is a mouse coronavirus which is really well studied in the laboratory setting for which there are a number of tools and which is safe to humans because it's a mouse-adapted virus. Making MHV coronavirus decorated with Sars-CoV-2 can be really a good first step towards making a virus that resembles Sars-CoV-2 on some level and that is likely to behave like it does naturally. But the fact is there'll probably be the generation of a whole slew of viruses that don't involve the MHV strain but a different one. There are various coronaviruses that infect us seasonally which are essentially nonpathogenic and those would be good candidates as well.

Barr: One of my other questions is: You spoke about it a little bit in the beginning, but what are the real-time implications of your work that are tangible for the American people to know? Why is this so important?

Compton: One reason why it's important is that IFITM-3 is what's known as an interferon stimulated gene. There are hundreds of interferon stimulated genes encoded by the human genome, and so this set of genes is meant to respond to viral infections and in some cases to inhibit virus replication. Our study contributes new information to this set of genes and provides us a clearer mechanism of how they function. Another reason that is perhaps more acute in terms of urgent need for information is, does that mean that interferons can be used as a treatment for COVID-19 or to prevent Sars-CoV-2 infection in the first place?

There's a lot of interest in this now. There are entire studies being performed to assess the role of interferon in humans. This is a tricky business because interferon can induce this set of antiviral genes as I mentioned, but interferon can also play a very important role in our adaptive immune response and can play an important role in what we call inflammation. Because of years and years of HIV studies, we know a lot about the pros and cons of interferon treatment, so we felt it was particularly pertinent to ask this question because IFITM-3 is an interferon-stimulated gene.

If one finds that an interferon-stimulated gene [ISG] promotes infection, this would be a reason to be cautious about using interferon in vivo. As I mentioned, IFITM-3 strongly promotes another human coronavirus, so the fact that we're seeing some antiviral potential of IFITM-3 against Sars-CoV-2 tells us that for this particular ISG, interferon treatment in vivo may not result in a strong enhancement of infection and an increase of the severity of disease. One of the major points for doing the study is trying to understand more about how interferon might be used in humans, whether we should use it, whether we should avoid it. In the case of studying IFITM-3 within that question, the fact that IFITM-3 has been shown to be the most important interferon stimulated gene during influenza, a virus infection, and so, because Sars-CoV-2 is also a respiratory virus, we have to kind of start with an assumption that it could be important.

That's really the basis for our study is to provide more information about these interferon-stimulated genes and how they may promote or inhibit virus infection. We include a number of experiments in our paper that show the effects of interferon treatment, and importantly interferon itself overall strongly inhibits Sars-CoV-2 infection of cells. That tells us that whatever those cells are hard-wired with, all of the induction of the ISGs overall results in a strong inhibition of Sars-CoV-2. We really needed to assess the outcome of that experiment as well.

So overall this tells us that interferon is antiviral against the virus, at least in a simple modified laboratory setting where we study just virus entry. That's really important information. Secondly, an important interferon-stimulated gene overall has a negative effect on Sars-CoV-2, but when you read between the lines, it's actually able to promote infection at certain points in the cell. We think that this is just providing appropriate information about interferon, the effects of interferon, and its potential usefulness. This is just one aspect that supports the idea that interferon could be useful for a treatment.

Barr: We're going to transition from your study to more about you. So, what has been your role in this study?

Compton: My role basically was to conceive the study and to start getting the gears turning in March 2020 while we had lockdown and while the normal business of the NCI was effectively shut down. At that point, there was an active effort to engage NIH investigators in studies relevant to Sars-CoV-2 and COVID-19 and, because of our interest in studying virus entry and the inhibitors of virus entry, it was very logical for us to propose this type of work. We had a lot of the existing tools to do this the right way and to do it really efficiently. Basically, how this worked is we proposed the subject of the study and it was essentially what I told you: to assess whether IFITM-3 promotes or inhibits Sars-CoV-2 infection. We did receive some research funds to do this through the NIAID Intramural Targeted Anti-COVID19 (ITAC) program and that's going to provide some support for us to continue these studies for the next two to three years. How this got going is simply asking the right questions, starting to ask our colleagues and our collaborators what we can do. In the case of this partnership with OSU, it came down to us having conversations of what we should and would like to do to meet the needs of COVID-19 research. It just so happened that Jacob Yount at OSU had invested time into setting up a BSL-3 [biosafety level 3] laboratory which did not exist in his institute prior to the pandemic. Because he had done that and because he had developed a system that would enable use of Sars-CoV-2 which is replication competent, he was really the ideal collaborator. Part of my role was getting him and his lab involved.

Barr: How did you meet him? You said you had worked with OSU before but were there other contenders who you thought about collaborating with?

Compton: Contenders, yes. And they're still a part of our portfolio of collaborators. The fact is we ended up moving forward with OSU simply because they were ready and able; they had the time and the resources and the personnel to commit to performing the study. That's really what is essential. Other collaborators who we're still working with on Sars-CoV-2 related work—including things related to this study—are USAMRIID, which is the U.S. Army Medical Research Institute for Infectious Diseases and which is based on my campus in Frederick, Maryland, at Fort Detrick, and NIAID at Rocky Mountain Laboratories in Hamilton, Montana. So basically, since March, I've built a group of people with whom we correspond regularly and with whom we have projects initiated. This installment that's published has manifested between my group and Jacob's group at OSU.

Barr: Can you speak a little about your team and what it's like to work with them and who they're comprised of?

Compton: I'm a tenure track investigator, which means that I'm relatively new to the NIH world and the lab opened its doors in 2017. It also means that I am working with a small group of people. In my lab, I have three postdoctoral fellows, a PhD student, and a post-baccalaureate. We are six people overall. In terms of what's been going on this year and this particular project, the work was done primarily by one of the postdoctoral fellows, Scarlett Shi. She is the first author on the publication, and she has recently been promoted to Research Fellow, which is essentially like a senior postdoctoral fellow who is federally employed. She has more responsibilities in the lab, not only performing lab management and training and organization, but she was the person who did a lot of the heavy lifting for this project and she continues to move it forward. The others in the lab have mostly stuck with projects that are related to HIV, influenza, and other pre-existing topics. A couple of them have also dabbled in some experiments to see whether what they're studying could be applicable to Sars-CoV-2. Since we have these tools available, we can apply them to any scientific question we want to. For the most part and for this paper, Scarlett was the person from my lab doing the work and with whom I worked closely on the manuscript. It was also an interesting situation because this paper resulted from a collaboration between two labs and two different locations. This can often lead to tricky situations when you try to allocate authorship and contributions. In this situation, we agreed on two "co-first" authors. So two people are at the head of the author list: Scarlett, from my lab, and Adam Kenney from Jacob Yount's lab. Adam Kenney is a PhD student at OSU. Both of them were the heavy lifters for this work, with Scarlett doing the HIV-based experimental work here in Frederick and Adam doing the work with genuine Sars-CoV-2 in a BSL-3 setting in Columbus, Ohio.

Barr: So during the pandemic, were you mostly on campus in your lab or were you home or combination and what was that like?

Compton: It's always been a combination because we started to propose ideas about Sars-CoV-2 research in March at the moment the lockdown occurred. We've had buns in the oven for a while and we've always had some presence in the lab, so I do about 50% work from home and about 50% work from the lab now. Actually, I'm doing less work in the lab per se and I'm really in my office now, which is unusual for me. This year looks very, very different but being in my office puts me in the building and that has been important for maintaining a lot of the lab infrastructure. We're also making sure that some of the experimental work of the other members of the lab can continue.

It's been kind of bittersweet in the sense that I've enjoyed spending half of my time remotely, because it has changed how I work and how I see things. I have all these new tools in my hands to do work, and so, on one level, we're working more efficiently. The fact that I'm not always physically present in the lab every day can be a good thing, because when I do speak with people in the lab, we do so in a more efficient manner. We try not to spend time with arguments, with disagreements. We simply kind of know how to do certain things better now and I think that that's something we'll continue to keep with us as we move forward. It has been hard on me not to be in the lab so often not just because that means I can't directly speak with the people in my lab, but because I can't do any work myself. Since 2017, I've always had my hands-on experiments and I would often pursue my own kind of experimental aim. I would contribute to each paper in the lab with my own hands and my own experiments. That was really beneficial for everyone. It allowed us to do things more quickly.

I haven't really been able to do that this year. I feel like I'm completely confined to my ability to communicate and to write and to just brainstorm ideas, which is not bad. It's allowed me to improve that aspect of my job. If I were in the lab all the time doing experiments, chances would be that I am not providing enough time for each person in my lab to supervise what they're doing in terms of reading papers, discussing experimental protocols, and moving forward. So overall, I think that there are certain things that we have learned during this time. I think this 50-50 teleworking and in person is going to allow us to take advantage of the best of both worlds.

Barr: So what have been other personal opportunities and challenges that have sort of come to light during the pandemic?

Compton: Definitely challenging would be the fact that some of the personnel of our campus staff at every level have not been able to be present and do their jobs as they were before. That has made every task more complicated from ordering materials, to having materials delivered. Things that involve construction and renovation are very challenging to do right now. These have been hard to swallow and those types of delays have been somewhat distracting. The fact is we have to accept them and simply find a way to make do with them. I should say that with my lab being based in Frederick I've been very pleased with how the infrastructure has remained intact. They've been able to really stay in business really well. I can't say how it is for other buildings on the main campus, but I think this has been one benefit of being in Frederick is that the organization in place here made it a little bit easier to respond to the pandemic. We don't have a strong clinical presence here as there's no hospital, there are very few members of the public who are present on our campus and so on one hand it made getting back to work a little bit easier. I'm thankful for the state of things here on our campus, and that despite some inconveniences and some frustration, it's perfectly acceptable.

In the long term I think that our ability to interact with staff on all levels is going to be improved because now we have these new tools and we can teleconference with each other on a moment's notice, we can do work remotely. All of these needs for computation can be done in ways that were not the case in 2019. I think we've all adapted really well and that's what we have to do is not consider how this has negatively impacted us, but we just have to consider how it is possible to adapt and to adapt for the better.

Barr: This is a fun question. What have you found that you could live without these past few months and what have you discovered that you really miss?

Compton: What I really miss is the opportunity to go to restaurants and go to cafes and participate in the community life like l used to and my wife used to, because that was not only a part of our personal lives but it was a part of our work lives. We really liked the idea of working from different locations and so were already doing some remote work before the pandemic hit. We were doing so by exploring neighborhoods, exploring cafes, going to cool public libraries. All of these types of public spaces that we really enjoyed has been the hardest thing and the thing that we've missed probably the most.

The other part of your question was: What do I like the most about what's changed? To be honest, I like that a lot of our meetings have gone virtual, not just conferences, but our personnel meetings. This year kind of has a silver lining in that I feel like I've been using my time much more efficiently in meetings that I was before and partly that's due to us being virtual. I really enjoy the fact that a lot of these in-person things that we were doing are done online which may sound surprising. I think that when you don't need to drive somewhere or take the metro somewhere to attend a meeting, and you can do other things while a meeting is going on, it is really advantageous for everyone. The fact that it completely opens up when you can have the meetings, you no longer are confined to a specific time of day just because of not having to require everyone's physical presence somewhere. I really have enjoyed what that has meant for us and for my program and for the other PIs in my program. I like the idea of what a meeting looks like now and the same goes for people in my lab.

Our lab meetings are different. l do miss the in-person aspect, but we do things in lab meetings now that were never possible before. We can all share something during a lab meeting; we can all contribute visuals at any moment; we can share links to each other on the screen. It actually pushed us to another level and on top of that I'm somewhat of a solitary person. There's been a lot of introspection that's been made possible by the absence of all of my other co-workers. Our building has always been open during this time and it's always been productive. The fact is that a lot of the personnel have been absent as they should be. I've also enjoyed that the building is simply a little bit quieter. It has changed a lot about how I think and work actually. For someone who enjoys quiet, that's been really nice despite the fact of what that means, namely, that silence is an eerie silence and it's generally something that's associated with something negative. The fact is it's just that the silver lining that exists is that we can kind of make our space our own, rethink our space, and turn it into a place where we can work in the best way possible. I think that is true for many of us.

Barr: Is there anything else you would like to share at this time as a scientist but also as a person living through the pandemic?

Compton: I'm quite optimistic about the future at the NIH and about my lab's place in the NIH because of the adaptation that occurred this year and how we're thinking how we work. It's going to be easier for me to interact with even more people on all campuses of the NIH because now we have kind of a common enemy and a common focus. We're going to have more potential for collaboration. It's even easier for us to collaborate now with teleconferencing. That is something I feel good about. It is situations like this where we can take full advantage of what the NIH has to offer in terms of personnel expertise and technology. That's going to be a major plus for my lab since it's a new lab. It is setting us on the right track for the future. I'm hopeful about how I can participate in the NIH as a whole.

Barr: I wish you the best of luck with your research and I wish you and your lab success and that you all continue to stay safe.

Compton: You, too. Thank you very much for speaking with me. I really enjoyed this.